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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/704,445	08/26/96	CHEN	B 202962001301

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EXAMINER	
HAUDA,K	
ART UNIT	**PAPER NUMBER**
1632	31

DATE MAILED: 05/12/99

Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/704,445	Chen et al.
Examiner	**Group Art Unit**
Karen M. Hauda	1632

☒ Responsive to communication(s) filed on *Feb 16, 1999* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-3, 5, 8-14, 17-19, and 21-40* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3, 5, 8-14, 17-19, and 21-40* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicant's amendment was filed February 16, 1999. Claims 1-3, 5, 8-14, 17-19, and 21-40 are pending.

Claim Rejections - 35 USC § 112

Claims 1-3, 5, 8-14, 17-19, and 21-40 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's specification enables a method of reducing the depletion of non-autologous hematopoietic cells in a mammal which lacks functional endogenous B- and T- cells comprising administering to the mammal an effective amount of dichloromethylene diphosphonate such that the number of endogenous macrophages are decreased to a level effective to reduce depletion of transplanted non-autologous hematopoietic stem cells.

Applicants argue that the claimed invention is enabled for immunocompromised mammals. Applicants direct the examiner to page 7 of the specification where immunocompromised animals include "humans, SCID mice, SCID-hu mice, CID horse and transgenic immunodeficient mice. Applicants argue that the therapeutically effective dose of dichloromethylene diphosphonate are

capable of extrapolation from the SCID-hu mouse model to humans. Applicant's arguments have been carefully considered, but are not deemed persuasive.

It is initially noted that applicant's specification does not specifically define "immunocompromised". When the term "immunocompromised" is viewed in its broadest sense, it encompasses mammals with even the slightest down regulation of immune function, such as a mammal with a cold, the flu, or an ear infection. As stated in the previous office action (pages 4-5), T-cells play a strong role in non-autologous hematopoietic cell rejection. Applicant's experiments in mice which lack **all** functional T- and B- cells is not correlative to treating mammals with functional T- and B- cells. Rejection of the non-autologous hematopoietic cells in mammals which have function T-cells is nearly assured (see Sykes et al. or Smith et al, for example), such that a reduction in depletion of the non-autologous hematopoietic cells is at best unpredictable. Thus, applicant's incorporation of the term "immunocompromised" into the claim language does not overcome the rejection of record because of the reasons set forth herein and in the previous office action.

Applicants additionally argue that any agent known in the art which **selectively** kills macrophages can be used to practice the claimed invention. However, the only agent disclosed in the specification is dichloromethylene diphosphonate. Applicants argue that other agents are taught by Van Rooijen and Claasen (1988). However, applicants have not made this reference of record, such that the Examiner can consider the enablement of other agents disclosed therein. Furthermore, Van Rooijen and Claasen (1988) have not been incorporated into the specification.

Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. In re de Seversky , 474 F.2d 671, 177 USPQ 144, (CCPA 1973). In addition to other requirements for an application, the referencing application should include an identification of the referenced patent, application, or publication. Particular attention should be directed to specific portions of the referenced document where the subject matter being incorporated may be found. MPEP 608.01(p). Applicant's specification fails to provide such referencing to Van Rooijen and Claasen. The disclosure of a single agent which **specifically** kills macrophages does not enable a claim to any agent known in the art, when neither the art or the specification identifies to one of skill in the art which agents (other than dichloromethylene diphosphonate) specifically kill macrophages. Neither L-leucine methyl ester or colloidal carbon have been shown to selectively deplete macrophages. It would have required undue experimentation for one of skill in the art to identify a reagent (other than Cl_2MDP) and determine its concentration for use *in vivo* such that it would selectively deplete endogenous macrophages in any and all mammalian species given the absence of teaching in applicants specification, the absence of known reagents in the art, the unpredictability of isolating a reagent which would selectively decrease endogenous macrophages in any and all mammals without undue experimentation, the breadth of the claims, and the quantity of experimentation which would be required to identify such a reagent. Thus, the rejection is maintained.

For the reasons presented above, the claimed invention is limited to a method of reducing the depletion of non-autologous hematopoietic cells in a mammal which lacks functional endogenous B- and T- cells comprising administering to the mammal an effective amount of dichloromethylene diphosphonate such that the number of endogenous macrophages are decreased to a level effective to reduce depletion of transplanted non-autologous hematopoietic stem cells; a non-human mammal which lacks functional endogenous T- and B- cells comprising human hematopoietic cells wherein the non-human mammal contains a decreased level of endogenous macrophages sufficient to reduce depletion of non-autologous hematopoietic cells, wherein the decreased level of endogenous macrophages is achieved by administering to the mammal an effective amount of dichloromethylene diphosphonate; and a method of improving or restoring engraftment efficiency for transplantation of a population of non-autologous hematopoietic cells in a host mammal which lacks functional endogenous T- and B- cells comprising transplanting non-autologous hematopoietic cells into a T- and B- cell deficient mammal in conjunction with administering to the mammal an effective amount of dichloromethylene diphosphonate which selectively decreases the number of endogenous macrophages in the host mammal.

The prior rejection of claims 1-3, 5, 7-18, 28 and 31 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of applicant's amendment.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen M. Hauda whose telephone number is (703) 305-6608.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian R. Stanton, may be reached at (703) 308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-2801.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Papers related to this application may be submitted to Group 160 by facsimile transmission. Papers should be faxed to Group 160 via the PTO Fax Center located in Crystal

Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is or (703) 305-3014 or (703) 308-4242.

Karen M. Hauda
Patent Examiner
April 27, 1999

BRIAN R. STANTON, PH.D
PRIMARY EXAMINER